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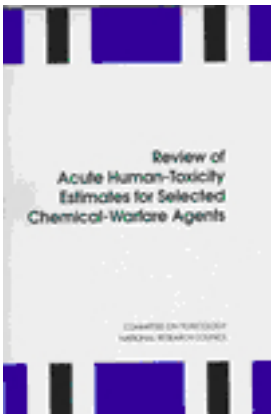

Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents

Committee on Toxicology, National Research Council
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"...recommends development of more scientifically sound toxicity values for various nerve agents such as sarin, the poison gas used in the Tokyo subway terrorist attack." National Research Council

Summary

No reliable acute-exposure[1] standards have been established for the particular purpose of protecting soldiers from toxic exposures to chemical-warfare (CW) agents. Some human-toxicity estimates are available for the most common CW agents—organophosphorus nerve agents and vesicants; however, most of those estimates were developed for offensive purposes (that is, to kill or incapacitate the enemy) and were intended to be interim values only.

The U.S. Army's original purpose for developing human-toxicity estimates for CW agents was to enable it to predict the number of casualties that would occur during an offensive action in which the goal was to kill or incapacitate a certain fraction of the enemy forces (for example, killing or incapacitating a minimum of 50% of the least-sensitive (most-resistant) individuals). Such an approach would actually result in more than half of the exposed individuals dying (the "bonus effect"), because a certain percentage of those exposed would be expected to be more susceptible than the least-sensitive individual. Thus, exposure under the Army's original estimates would result in substantial "over-kill." These estimates understate the toxicity of the agents and therefore are inappropriate for protecting soldiers.

[1] A one-time, short-term exposure, for example, under

Because of the possibility of a chemical attack by a foreign power, the Army's Office of the Surgeon General asked the Army's Chemical Defense Equipment Process Action Team (CDEPAT) to review the toxicity data for the nerve agents GA (tabun), GB (sarin), GD (soman), GF, and VX, and the vesicant agent sulfur mustard (HD) and to establish a set of exposure limits that would be useful in protecting soldiers from toxic exposures to those agents. In the 1994 report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier*, the team concluded that some of the existing human-toxicity estimates are too high and are inappropriate for use in protecting soldiers. In those cases, CDEPAT proposed new estimates for various routes of exposure—percutaneous vapor, vapor inhalation, and percutaneous liquid exposures. The proposed human-toxicity estimates are only for healthy male military personnel. They must not be used for civilians.

Before making a decision on acceptance of the human-toxicity estimates proposed by CDEPAT, the Department of the Army requested that the National Research Council (NRC) independently review the CDEPAT report to determine the scientific validity of the proposed estimates. The NRC assigned this project to the Committee on Toxicology (COT) of the Board on Environmental Studies and Toxicology. The COT convened the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, which prepared this report. Members of the subcommittee were selected for their recognized expertise in the fields of toxicology, medicine, pathology, biostatistics, and risk assessment. The subcommittee was charged to review the Army's proposed human-toxicity estimates for GA, GB, GD, GF, VX, and HD. Specifically, the subcommittee was charged with the following tasks:

1. Review the scientific protocols and quality of the toxicity data used in revising the human-toxicity estimates for acute exposures.
2. Review the toxicity estimates for mild and nonsevere effects and for severe and lethal effects.
3. Review the methods used in deriving the human-toxicity estimates for acute exposures.
4. Determine the appropriateness of the assumptions made in deriving the human-toxicity estimates for acute exposures.

The subcommittee was not asked to recommend new toxicity estimates

or to address the policy or operational consequences of lowering the proposed human-toxicity estimates. The subcommittee's evaluations of CDEPAT's proposed estimates for GA, GB, GD, GF, VX, and HD are summarized in Tables I through 6.

The subcommittee's conclusions concerning the scientific validity of the proposed CDEPAT estimates are grouped in four categories: (1) some estimates were judged to be scientifically valid; (2) other estimates were judged adequate to serve as interim estimates until further research is conducted; (3) some estimates need to be lowered; and (4) a few estimates need to be raised.

The toxicity data that CDEPAT used to derive its proposed estimates were generated primarily from a data base developed from the 1930s to the 1960s. The existing human-toxicity estimates were based on experiments performed 30–40 years ago using various animal species in often poorly controlled studies with vastly different protocols. In reviewing the available toxicity data for the six CW agents, the subcommittee recognized that the quality of the relevant toxicity data is marginal, but it also recognized that the Army needs "best estimates" to protect its troops from exposure. For each chemical agent, data were available for only a few adverse health effects, such as death, incapacitation, cholinesterase (ChE) inhibition, miosis (a decrease in pupil size), and rhinorrhea (running nose), vesication, and erythema. Thus, even though the subcommittee concluded that some of CDEPAT's proposed estimates are scientifically valid, those conclusions are based on a limited toxicity data base. By current standards of toxicology, the toxicity data base for the agents is inadequate, and such inadequacy is a major obstacle to the Army in developing human-toxicity estimates with statistical confidence and in developing risk-management strategies.

The subcommittee recommends that the Army convene an expert panel to develop a research strategy for deriving more scientifically sound toxicity values for the agents of concern. The panel should first consider the use of such techniques as structure-activity relationships, the uncertainty factors, and in vitro systems for estimating human-toxicity values for CW agents.

If these approaches do not appear to be useful, animal and human experimentation may be recommended. Although additional research is clearly desirable to provide improved confidence in existing data, such research should not be performed on laboratory animals until expert judgment documents the need on a case-by-case basis. It must be documented that the data to be obtained from laboratory animals is needed to make a significant improvement in the protection of human health.

TABLE 1 Evaluation of Human-Toxicity for GA

		Human-Toxicity Estimates for GA			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	20,000 mg-min/m^3	15,000 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by human data
	Inhalation, vapor	135 mg-min/m^3	70 mg-min/m^3	Proposed estimate should be lowered	Because of inadequate data on GA for this route, CDEPAT derived the estimate by assuming that GA is 0.5 times as toxic as GB; approach reasonable but estimate should be lowered because of recommended lowering of LCt_{50} for GB for this route; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	2,000 mg-min/m^3	Proposed estimate is scientifically valid	ChE inhibition data used for proposing new recommendation
Severe effects	Inhalation, vapor	None	50 mg-min/m^3	Proposed estimate should be lowered	CDEPAT's proposed estimate based on a study that indicated the ratio of ICt_{50}[e]/LC_{50} is 0.75; that assumption used to establish ECt_{50}. for severe effects; the subcommittee recommends that the ECt_{50} estimate be lowered to correspond to the lowered estimate for LCt_{50}; further research recommended
Mild effects	Inhalation, vapor	0.9 mg-min/m^3	0.5 mg-min/m^3	Proposed estimate should be raised	Human data show that humans can tolerate higher exposures; further research recommended

Toxicity Type	Route and Form of Exposure	Human-Toxicity Estimates for GA: Existing Estimates	Human-Toxicity Estimates for GA: CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LD_{50}[c]	Percutaneous, liquid	1,500 mg for 70-kg man	1,500 mg for 70-kg man	Proposed estimate should be lowered	No uncertainty factors used in lieu of limited animal data for proposed estimate; further research recommended
ED_{50}[d]	Percutaneous, liquid	None	880 mg for 70-kg man	Proposed estimate should be lowered	In the absence of adequate human or animal data for this effect, CDEPAT established the estimate by assuming ID_{50}[f]/LD_{50} ratio of 0.6 to estimate ED50; the subcommittee recommends that the ED_{50} estimate be lowered to correspond to the lowered estimate for LD_{50}; further research recommended

Ct_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.
ICt_{50}: Vapor exposure that produces incapacitation in 50% of the exposed population.
ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 2 Evaluation of Human-Toxicity Estimates for GB

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	15,000 mg-min/m^3	10,000 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by studies in monkeys and humans
	Inhalation, vapor	70 mg-min/m^3	35 mg-min/m^3	Proposed estimate should be lowered	Estimate too high because human studies show 100% lethality at 40 mg-min/m^3
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	1,200 mg-min/m^3	Proposed estimate is scientifically valid	Estimate supported by studies of ChE inhibition in humans; further research recommended
Severe effects	Inhaiation, vapor	35 mg-min/m^3	25 mg-min/m^3	Proposed estimate should be lowered	ECt_{50}/LCt_{50} ratio of 0.7 used to develop estimate; LCt_{50} for this route of exposure was lowered; therefore, ECt_{50} should be lowered correspondingly; further research recommended
Mild effects	Inhalation, vapor	2 mg-min/m^3	0.5 mg-min/m^3	Proposed estimate should be raised	No effects in humans at 0.5 mg-min/m^3; effects begin to appear at ≈ 2 mg-min/m^3; further research recommended
LD_{50}[c]	Percutaneous, liquid	1,700 mg for 70-kg man	1,700 mg for 70-kg man	Low confidence in proposed estimate; proposed estimate should serve as interim value	Estimate based on a ratio of ChE inhibition in rabbits and humans; however, human data concerning the relation between ChE inhibition and adverse effects are inconsistent; further research recommended

		Human-Toxicity Estimates for GB			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
ED_{50}[d] severe effects	Percutaneous, liquid	None	1,000 mg for 70-kg man	Proposed estimate should serve as interim value	In the absence of adequate data on GB for this effect, CDEPAT assumed that the ratio of lD_{50}[c]/LD_{50} is 0.6 and used that to estimate the ED_{50} values; further research recommended

Lct_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.

Ect_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).

LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.

ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 3 Evaluation of Human-Toxicity Estimates for GD

		Human-Toxicity Estimates for GD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	None	2,500 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate based on assumption that GD is 4 times more toxic than GB for percutaneous exposure
	Inhalation, vapor	70 mg-min/m^3	35 mg-min/m^3	Proposed estimate should be lowered	Proposed estimate based on the assumption that GD and GB are equipotent via this route; subcommittee recommends that LCt_{50} estimate for GD be lowered to correspond to lowered estimate for GB; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	300 mg-min/m^3	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate based on assumption that GD is 4 times more toxic than GB for percutaneous exposure; further research recommended
Severe effects	Inhalation, vapor	35 mg-min/m^3	25 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate human or animal data, proposed estimate based on assumption that potencies of GD and GB are comparable; ECt_{50} estimate for GD should be lowered to correspond to the lowered estimate for GB; further research recommended

Toxicity Type	Route and Form of Exposure	Human-Toxicity Estimates for GD: Existing Estimates	Human-Toxicity Estimates for GD: CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
Mild effects	Inhalation, vapor	None	0.2 mg-min/m^3	Proposed estimate should be raised	In the absence of adequate human or animal data, proposed estimate based on assumption that GD is 2.5 times more potent than GB for miotic effects; subcommittee recommends that the LCt_{50} estimate for GD be raised to correspond to the recommended raised estimate for GB; further research recommended
LD_{50}[c]/ED_{50}[d]	Percutaneous, liquid	350 mg for 70-kg man	350 mg for 70-kg man	Proposed estimate should serve as an interim value	Because of wide range of LD50 values in animals, subcommittee's confidence in the proposed estimate is low; CDEPAT's proposed estimate of 350 mg for 70-kg man should serve as an interim value; further research recommended
Severe effects	Percutaneous, liquid	None	200 mg for 70-kg man	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate was derived using the ID_{50}[e]/LD_{50} ratio of 0.6; the subcommittee recommends that CDEPAT's proposed estimate serve as an interim value; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.

[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).

[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.

[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

[e] ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 4 Evaluation of Human-Toxicity Estimates for GF

		Human-Toxicity Estimates for GF			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	15,000 mg-min/m^3	2,500 mg-min/m^3	Proposed estimate should serve as an interim value	Rationale for the CDEPAT estimate not supported by data; further research recommended
	Inhalation, vapor	None	35 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate data, proposed estimate based on assumption that GF, GD, and GB are equipotent; approach is reasonable; because LCt_{50} for GB was recommended to be lowered, proposed value for GF should be lowered correspondingly; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	300 mg-min/m^3	Proposed estimate should serve as an interim value	Proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended
Severe effects	Inhalation, vapor	None	25 mg-min/m^3	Proposed estimate should be lowered	In the absence of adequate data, proposed estimate based on assumption that GF, GD, and GB are equipotent; approach is reasonable; because ECt_{50}[s] for severe effects for GB and GD were recommended to be lowered, proposed value for GF should be lowered correspondingly; further research recommended

Toxicity Type	Route and Form of Exposure	Human-Toxicity Estimates for GF: Existing Estimates	Human-Toxicity Estimates for GF: CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
Mild effects	Inhalation, vapor	None	0.2 mg-min/m^3	Proposed estimate should be raised	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; because ECt_{50} for mild effects for GD was recommended to be raised, proposed value for GF should be raised correspondingly; further research recommended
LD_{50}[c]	Percutaneous, liquid	None	350 mg for 70-kg man	Proposed estimate should serve as an interim value	In the absence of adequate human or animal data, proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended
ED_{50}[d]					
Severe effects	Percutaneous, liquid	None	200 mg for 70-kg man	Proposed value should serve as an interim value	In the absence of adequate human or animal data, the proposed estimate based on assumption that GF and GD are equipotent; approach is reasonable; further research recommended

[a] LCt_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.

[b] ECt_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).

[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.

[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

TABLE 5 Evaluation of Human-Toxicity Estimates for VX

		Human-Toxicity Estimates for VX			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	None	150 mg-min/m^3	Proposed estimate should be considered an interim value	Degree of confidence in data is low to moderate; further research recommended
	Inhalation, vapor	30 mg-min/m^3	15 mg-min/m^3	Proposed estimate should be lowered	Degree of confidence in data is low to moderate; further research recommended
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	10 mg-min/m^3	Proposed estimate should be considered an interim value	Degree of confidence in data is low; a no-observed-adverse-effect level (NOAEL) was not defined; further research recommended
Severe effects	Percutaneous, vapor	None	25 mg-mill/m^3	Proposed estimate should be considered an interim value	Degree of confidence low to moderate; further research recommended
	Inhalation, vapor	25 mg-min/m3	10 mg-min/m3	Proposed estimate should be considered an interim value	Insufficient data; further research recommended
Mild effects	Inhalation, vapor	0.09 mg-min/m^3	0.09 mg-min/m^3	Proposed estimate is scientifically valid	Available human data support the proposed estimate
LD_{50}[c]	Percutaneous, liquid	10 mg/70-kg man	5 mg/70-kg man	Proposed estimate should be lowered	Animal data indicate that the proposed estimate is too high; furthermore, no uncertainty factor used in lieu of variability associated with dermal penetration of various regions of body; further research recommended

		Human-Toxicity Estimates for VX			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
ED_{50}[d] severe effects	Percutaneous, liquid	5 mg/70-kg man	2.5 mg/70kg man	Proposed estimate should be lowered	The ED_{50} is based on the ID_{50}[e]/LD_{50} ratio; the subcommittee recommends that the LD_{50} be lowered, therefore, the ED_{50} should be lowered correspondingly; further research recommended

Lct_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.

Ect_{50}: Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).

LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.

ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

ID_{50}: Liquid dose causing incapacitation in 50% of the exposed population.

TABLE 6 Evaluation of Human-Toxicity Estimates for HD

		Human-Toxicity Estimates for HD			
Toxicity Type	Route and Form of Exposure	Existing Estimates	CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
LCt_{50}[a]	Percutaneous, vapor	10,000 mg min/m^3	5,000 mg-min/m^3	Proposed estimate should be lowered	Estimate might be too high because data from the most-sensitive species (rats and mice) not used; further research recommended
	Inhalation, vapor	1,500 mg min/m^3	900 mg-min/ m^3	Proposed estimate is scientifically valid	CDEPAT averaged LCt^{50} data in several animal species; in the absence of data on humans, that approach is reasonable
ECt_{50}[b]					
Threshold effects	Percutaneous, vapor	None	50 mg-min/ m^3 (moderate temperature); 25 mg-min/ m^3 (hot temperature)	Proposed estimates should serve as interim values	In the absence of details on studies on which estimates were based, proposed estimate should be considered interim value; further research recommended
Severe effects	Percutaneous, vapor	2,000 mg-min/ m^3 (moderate temperature) 1,000 mg min/ m^3 (hot temperature)	500 mg-min/ m^3 (moderate temperature); <200 mg-min/m^3 (hot temperature)	Proposed estimates are scientifically valid	Estimates based on human studies

Toxicity Type	Route and Form of Exposure	Human-Toxicity Estimates for HD: Existing Estimates	Human-Toxicity Estimates for HD: CDEPAT's Proposed Estimates	Subcommittee's Evaluation of Proposed Estimates for GA	Rationale for Subcommittee's Evaluation
Ct_{50}[a]	Inhalation, vapor	200 mg-min/m^3 (moderate temperature)	100 Mg-Min/m^3 moderate temperature)	Proposed estimate is scientifically valid	Proposed estimate supported by human data
Mild effects	Inhalation, vapor	>50 mg min/m^3	25 mg-min/m^3	Proposed estimate is scientifically valid	Proposed estimate supported by human data
LD_{50}[c]	Percutaneous, liquid	7,000 mg for 70-kg man	1,400 mg for 70kg man	Proposed estimate is scientifically valid	Proposed estimate supported by a study in dogs
ED_{50}[d] Severe effects	Percutaneous, liquid	None	610 mg for 70-kg man	Proposed estimate is scientifically valid; however, it should be rounded to 600 mg for a 70-kg man to avoid appearance of precision that is not there	Proposed estimate supported by human data

[a] Lct_{50}: Vapor exposure that produces lethality in 50% of the exposed animals. Ct refers to the product of concentration (c) and exposure time (t). Note that Ct is not necessarily a constant.
[b] ECt_{50} Percutaneous vapor exposure or inhalation vapor exposure causing a defined effect (e.g., incapacitation, severe effects, mild effects, threshold effects).
[c] LD_{50}: Liquid dose causing lethality in 50% of the exposed animals.
[d] ED_{50}: Liquid dose causing a defined effect in 50% of the exposed animals.

The experimental designs should include the following:

- Define if and when experiments with humans are appropriate.
- In the absence of human experimentation, define the most appropriate animal model for each specific toxicity value and agent, including the end points to be observed.
- Define the adequacy of the design in determining the toxicity values for healthy female as well as healthy male military personnel.
- Define the requirements for observation of reversibility of adverse health effects.
- Identify adverse health effects at the low end of the dose-response curve to determine threshold exposure levels.
- Identify confidence limits for the proposed estimates as a measure of the uncertainty of the estimated incidence of toxic effects.
- Identify potentiation or antagonistic effects from exposures to mixtures of chemical agents.
- Identify more-sensitive biological markers of exposure and effects for CW agents.

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Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

Due to the Existence of large stocks of chemical-warfare (CW) agents, their easy producibility from ordinary industrial chemicals, and their potential lethal effects, there is a critical need to determine as precisely as possible the exposure levels at which CW agents cause toxic effects. This information could aid in protecting soldiers in the event of a CW attack.

This report, by the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents of the National Research Council's Committee on Toxicology, is intended to assist the U.S. Army by assessing the scientific validity of existing human-toxicity estimates for several CW agents. The estimates considered in this report were proposed recently in the Army's Chemical Defense Equipment Process Action Team (CDEPAT) report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier* (1994). The report was authored by S.A. Reutter, Ph.D., and W.A. Wade, D.V.M.; it is classified "secret" and can be obtained only with permission from the director of the U.S. Army Edgewood Research, Engineering and Development Center, Edgewood, Md.

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We are grateful for the assistance of the National Research Council staff in preparing this report. Staff members who contributed to this effort are Paul Gilman, executive director of the Commission on Life Sciences; James J. Reisa, director of the Board on Environmental Studies and Toxicology; Carol A. Maczka, program director for toxicology and risk assessment; Ruth E. Crossgrove, editor; Lucy V. Fusco, project assistant, and Catherine M. Kubik, senior program assistant. We especially wish to recognize the major contributions of the project director, Kulbir S. Bakshi, who directed the preparation of the subcommittee's report. His knowledge of the scientific and technical literature and his tireless efforts to obtain information and to organize the study plan, the subcommittee meetings, and the subcommittee's report aided in the successful completion of the project.

Finally, we would like to thank all the members of the subcommittee for their dedicated efforts throughout the development of this report.

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Introduction and Background

The U.S. Army's Chemical Defense Equipment Process Action Team (CDEPAT) recently conducted an extensive review of the scientific basis for toxicity estimates in use by the Army for several chemical-warfare (CW) agents: GA, GB, GD, GF, VX, and HD. Following a detailed analysis of the toxicity of these agents and using contemporary methods of analysis, CDEPAT concluded that many of the human-toxicity estimates in use would not protect the soldier adequately (CDEPAT 1994). Recalculations of the potencies of several of the CW agents indicate that their potencies are greater than previously determined. As a result, lower exposure levels of CW agents are expected to elicit adverse effects.

Before deciding whether to implement CDEPAT's recommendations, the U.S. Department of the Army requested that the National Research Council (NRC) independently review the CDEPAT report entitled *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates for Defending the Soldier*. The NRC assigned the project to the Committee on Toxicology (COT) of the Board on Environmental Studies and Toxicology. The COT convened the Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, which conducted the study and prepared this report. Subcommittee members were chosen for their expertise in several specialties, including

toxicology, medicine, pathology, biostatistics, and risk assessment. The subcommittee was charged with determining the scientific validity of CDEPAT's proposed human-toxicity estimates for CW agents for various routes of exposure (that is, percutaneous vapor exposures, vapor inhalation exposures, and percutaneous liquid exposures). The report considers only acute[1] exposures and acute effects. It should be noted that the human-toxicity estimates for the CW agents were proposed for healthy adult male soldiers only. They must *not* be used for the general population. Specifically, the subcommittee was charged with the following tasks:

1. Review the scientific protocols and the quality of the toxicity data used in revising the human-toxicity estimates for acute exposures.
2. Review the toxicity estimates for mild and nonsevere effects and for severe and lethal effects.
3. Review the procedures used in deriving the human-toxicity estimates for acute exposures.
4. Determine the appropriateness of the assumptions made in deriving the human-toxicity estimates for acute exposures.

In reviewing the toxicity data and the proposed human-toxicity estimates for acute exposures, the subcommittee evaluated the quality of the data, the appropriateness of the procedures used in obtaining the estimates, and the assumptions made in deriving them. The subcommittee also determined whether the supporting documentation justified the proposed recommendations and whether the studies and toxicity end points were appropriate for deriving the toxicity estimates. In reviewing the proposed human-toxicity estimates, the subcommittee reviewed only the toxicity information presented in the CDEPAT report. It did not perform an independent literature search, nor did it review any data other than those presented in the report. In addition, the subcommittee was not asked to recommend new estimates or to address the policy or operational consequences of the proposed lower human-toxicity estimates.

The exposures used in the estimates are defined as follows:

- LCt_{50} is the exposure to a vapor causing lethality in 50% of a given population and is expressed as the product of air concentration (c), in

[1] A one-time, short-term exposure, for example, under